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Chapter 1: General introduction

This thesis focusses on the relationship between allergy and soil-transmitted helminths (STHs). The term allergy is collectively used for atopic diseases and allergic sensitization in this thesis. Atopic diseases are inflammatory disorders characterized by hypersensitivity of the immune system to harmless environmental allergens. Atopic diseases include asthma, allergic rhinoconjunctivitis (hayfever), and atopic dermatitis (eczema). Allergic sensitization or atopy is the tendency to react to allergens and develop atopic diseases. Allergy is a worldwide problem, with asthma being the most common chronic disorder in children, and it poses a significant burden on the individual patient, family, healthcare services, and society.

STHs are an important group of parasitic worms that often result in chronic infections in humans. The most important STHs are *Ascaris lumbricoides* (roundworm), *Trichuris trichiura* (whipworm) and hookworm (mine worm). More than two billion people worldwide are infected with these worms of which mostly children. STH infections cause malnutrition, anaemia, reduction in iron status, poor growth and delayed cognitive development.

The prevalence of allergy has increased strongly in the last decades in affluent countries while it remains relatively uncommon in non-affluent countries. On the other hand, in these non-affluent countries STH infections remain an important problem while they are now uncommon in affluent countries. A causal relationship has been assumed between these opposite trends. This is part of the so-called hygiene hypothesis which assumes that experiencing childhood infections influences the immune system in such a way that these infections can reduce the tendency to develop allergy/ immune disorders.

The relationship between STHs and allergy has been the focus of much epidemiological and immunological research. So far, research has provided conflicting evidence with studies showing that STH infections either promote, inhibit, or are unrelated to allergy. However, these results are mostly based on cross-sectional research. Therefore, the aim of this thesis is to assess within epidemiological studies the longitudinal effect of STH infections on allergy. The studies presented in this thesis have been performed in a cohort of Cuban schoolchildren, aged 4-14 at baseline, who were followed from 2003/2004 up to 2007. Allergy and STH infection status were evaluated every six to twelve months and STH infected children were treated with a single dose of 500 mg mebendazole, an anthelmintic drug. Atopic diseases were diagnosed using a validated questionnaire and allergic sensitization by skin prick testing. STH infection was assessed by detecting their eggs in stool.

Chapter 2-6: Study results

Firstly, in **Chapter 2**, the effectiveness of the periodic selective treatment regime for the deworming of schoolchildren in a low endemic setting was evaluated. This regime was found to be effective in reducing the number of STH infections in Cuban schoolchildren. The treatment was most effective for *A. lumbricoides*, followed by *T. trichiura* and least effective for hookworm.

The effect of deworming on the development of allergy was assessed in **Chapter 3**, to determine whether deworming would increase the prevalence of allergy as expected. However, atopic diseases did not increase and asthma even decreased after deworming. Only allergic sensitization increased after deworming but this increase was only temporary.

In **Chapter 4** changes over time in STH infection status, influenced by deworming and (re)infection, were related to changes in allergy status; also possible species-specific effects were assessed. The results indicated that (re)infection with *A. lumbricoides* and *T. trichiura* led to the development of atopic diseases while only hookworm seemed to be protective. An opposite effect was observed for allergic sensitization.

A prediction model was developed in **Chapter 5** to determine which common –environmental- risk factors were predictors for the development of asthma. Asthma status was related to a set of common risk factors. This model indicated that only antibiotics use, family history of atopic diseases and allergic sensitization predicted asthma development. STH infection did not play a role.

Finally, the effect of the economic circumstances during the Cuban ‘Special Period’ in the nineties on atopic diseases occurrence a decade later was assessed in **Chapter 6**. The crisis among others affected infectious diseases and nutrition. Children were divided into exposure groups according to birth date. Children who experienced the crisis during infancy and early childhood had less atopic diseases later in childhood than the children who did not experience the crisis. This suggests that factors related to this economic crisis might prevent the development of atopic diseases.

Chapter 7: General discussion

Periodic selective treatment with 500 mg mebendazole for the deworming of schoolchildren seems effective in low endemic settings. Still, not many well-designed studies evaluating the effectiveness of different selective treatment regimes have been performed while more of them are necessary to make sound policy decisions on the best regime in low endemic areas.

Based on the results of the longitudinal studies in this thesis and previous research by others, deworming of schoolchildren is unlikely to promote allergy. The same results also do not provide strong evidence in favour of the hypothesis that STH infections in schoolchildren protect against the development of allergy. Furthermore, the current worldwide trends point towards a limited role of (STH) infection on allergy. While the infectious disease prevalence is still decreasing, there are indications that allergy prevalence after decades of increase has reached a plateau and is even decreasing in some, especially affluent, countries. Therefore, further research is still needed to determine if and to what extent STH infection exert an effect on allergy development. This research should focus on or pay attention to the following aspects:

- *Underlying mechanisms in species-specific effects and their effect on atopic diseases as opposed to allergic sensitization*

The results of this thesis and other research indicate that probably only hookworm has a protective effect on atopic disease development while this is not the case for *A. lumbricoides* and *T. trichiura* and that the effect of the STHs is opposite for allergic sensitization.

- *Combining risk factors to predict or determine allergy development*

Research on the hygiene hypothesis has focussed mostly on individual associations of certain risk factors –including STH infections– with allergy while it is multifactorial in origin. Therefore, more research should be performed on which combinations of risk factors determine allergy development. An interesting topic could be the combined effect of nutritional status and STH infection on allergy. Undernutrition and helminth infections have a similar geographical distribution with the same individuals often experiencing both conditions concurrently. Furthermore, the prevalence of both allergy and obesity has concurrently increased in the last decades.

- *Change in study population*

While most research on allergy, including the research in this thesis, has been performed in schoolchildren, it has become clear that the strongest effect of (STH) infections and other factors is expected in infancy and early childhood. Therefore, the most important change is that future research should focus on pre-school children or preferably birth cohorts.

In conclusion, the relationship between STH infections and allergy remains inconclusive. The effect of STH infection on allergy seems limited in schoolchildren and research should focus more on the effects in infancy and early childhood thereby concentrating on species-specific effects and the combined effect of risk factors on atopic diseases and this must be set against the effects on allergic sensitization.